Povidone–iodine: use in hand disinfection, skin preparation and antiseptic irrigation

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ABSTRACT

Iodine and its antibacterial properties have been used for the prevention or management of wound infections for over 150 years. However, the use of solutions (tincture) of iodine has been replaced by the widespread use of povidone–iodine, a water-soluble compound, which is a combination of molecular iodine and polyvinylpyrrolidone. The resultant broad spectrum of antimicrobial activity is well documented and its efficacy, particularly in relation to resistant micro-organisms such as methicillin-resistant *Staphylococcus aureus*, has been shown. In the clinical environment, there is no general agreement regarding the 'best' antiseptic and the practice varies widely. This article reviews the studies that have assessed the efficacy of povidone–iodine in hand disinfection and skin preparation and its use as an antiseptic irrigant. Although there is a distinct lack of well-designed, randomised controlled trials evaluating antiseptic efficacy, selection should be based on the next best available evidence. This evidence suggests that the use of povidone–iodine as an agent of choice is dependent on the clinical need but is also likely to be influenced by personal preference.

Key words: Antiseptic • Hand disinfection • Irrigation • Povidone-iodine • Skin preparation

Key Points

- this article reviews the studies assessing the efficacy of povidone–iodine in hand disinfection and skin preparation and its use as an antiseptic irrigant

INTRODUCTION

Bernard Courtois first discovered the element iodine in 1811, and its antibacterial properties have since been used to cure or prevent infection in wounds for over 150 years; a preparation of iodide was first used in the treatment of wounds in 1839 (1). Natural products with high iodine content, such as seaweed extracts and oysters, were used in the American Civil War and during Napoleon's Egyptian campaign (2). However, aqueous or alcoholic (tincture) solutions of iodine were associated with skin irritation and excessive staining (3) and fell out of favour until the 1950s, when polyvinylpyrrolidone-iodine (PVP-I or povidone–iodine) was introduced as a water-soluble compound, resulting from the combination of molecular iodine and polyvinylpyrrolidone (4). This article reviews the studies assessing the efficacy of povidone–iodine in hand disinfection and skin preparation and its use as an antiseptic irrigant.

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CHEMICAL PROPERTIES

Povidone–iodine is an example of an iodophor, a complex of iodine and a solubilising carrier, which acts as a reservoir of 'free' active iodine (3). Iodine is complexed by polyvinylpyrrolidone and iodide through a hydrogen bond between the two pyrroles (5), but a small amount of free iodine is constantly released and remains in dynamic equilibrium with the complex. The free iodine is the bactericidal component, and its levels are dependent on the concentration of the povidone–iodine solution. It follows a bell-shaped curve: starting from a 10% solution [1 part per million (ppm) of free iodine], the content of non complexed free iodine increases as the dilution increases, reaching a maximum value at about 0·1% strength solution (1:100 dilution), but then decreases again with further dilution (6). This correlates with in vitro studies that show the paradoxical effect of increased antimicrobial action as the degree of dilution increases until dilutions of above 1:100, after which the germicidal activity decreases again (7).

Povidone–iodine (Betadine®) is available in a range of antiseptic formulations (8): the most commonly used are as an aqueous solution (10% PVP-I), an alcoholic solution (10% PVP-I) for quick-drying purposes and a surgical scrub (7·5%) in a non ionic surfactant basis for lather-forming purposes. The 10% aqueous povidone–iodine contains 90% water, 8·5% povidone and 1% available iodine and iodide (5), with a free iodine concentration of approximately 1 ppm. The 7·5% povidone–iodine provides 0·75% available iodine. Povidone–iodine is also commercially available as a dry powder spray (2·5% PVP-I) and as an ointment (10% PVP-I).

IN VITRO ANTIMICROBIAL ACTIVITY AND MECHANISM OF ACTION

The polyvinylpyrrolidone component of PVP-I increases the antimicrobial efficiency of iodine; it delivers the iodine directly to the bacterial cell surface as a result of its affinity to cell membranes (5). Once at the cell membrane, iodine rapidly penetrates into micro-organisms (3) and targets key groups of proteins, nucleotides and fatty acids in the cytoplasm and cytoplasmic membrane. Molecules required for survival are inactivated, resulting in cell death within a matter of seconds (5,9). Iodine and iodophors have a wide range of activity against Gram-positive and Gram-negative bacteria, tubercle bacilli, fungi, protozoa and viruses, as well as some activity against bacterial spores (5,10). The antiviral mechanism of action of iodine is not clear. However, lipid-enveloped viruses are thought to be more sensitive than non lipid-enveloped viruses and parvoviruses (3). Iodophors are considered to be less active than tinctures of iodine against certain fungi and spores (11) and are rapidly neutralised in the presence of organic matter such as blood, sputum or pus (12). Manufacturer's data show that iodophors are bactericidal, virucidal, fungicidal and tuberculocidal but are not sporicidal at recommended use dilutions (11).

Several in vitro studies have investigated the antimicrobial activity of povidone–iodine against different strains of bacteria. The majority of assessments of antiseptic activity have used reference and laboratory strains, which may have little similarity to clinical isolates (13). The in vitro bactericidal activity of Betadine skin antiseptic (10% PVP-I) and Betadine surgical scrub (4% PVP-I) was investigated against a collection of 504 bacterial strains isolated from nosocomial infections during routine clinical investigations (13). Bactericidal activity is measured using logarithmic reduction factors (LRFs) of colony-forming units, achieved over a range of exposure times and antiseptic concentrations, with a 5 LRF of challenge inoculum used as the minimum criterion of bactericidal activity (14). None of the enterococci, methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-resistant Gram-negative bacilli were resistant to either PVP-I preparation (13). The activity against MRSA confirmed the findings from a previous study, which showed that 10% PVP-I antiseptic solution exhibited superior killing effect, whether measured by rate of kill or final LRF achieved, against 33 clinical isolates of MRSA, when compared with an alternative antiseptic, chlorhexidine (CHX) (4% Hibiscrub or 20% Hibitane) (15). In another study, four strains of MRSA and two strains of methicillin-sensitive *Staphylococcus aureus* were exposed to 10% PVP-I, 0·5% CHX and 0·5% CHX in 80% ethanol (16). Although there was a significantly greater reduction in mean colony counts with 10% PVP-I compared with 0·5% CHX after 15- and 30-second exposures, the bactericidal activity of 0·5% CHX with ethanol was found to be the most potent and most rapid against these strains, with no organisms growing at all after exposure.

However, the superiority of PVP-I over CHX against antiseptic-resistant species has been shown (17); PVP-I showed high bactericidal activity against all the test strains after 30 seconds of exposure, and strains that acquired resistance against one antiseptic showed cross-resistance to all antiseptics except for PVP-I. Similar tests confirmed the efficacy of PVP-I against 20 strains of two Gram-negative bacteria (18), including resistant strains of both species, whereas CHX required greatly

Key Points

- the antiviral mechanism of action of iodine is not clear
- several *in vitro* studies have investigated the antimicrobial activity of povidone–iodineagainst different strains of bacteria; the majority of assessments of antiseptic activity have used reference and laboratory strains, which may have little similarity to clinical isolates

Key Points

- both *in vitro* and *in vivo* studies are important in developing an insight into the actual efficacy of these products
- the use of povidone–iodine in clinical studies is reviewed in this article with respect to three of its major applications:
  (i) Hand-washing and disinfection
  (ii) Skin preparation prior to invasive procedures
  (iii) Antiseptic irrigation

increased time to kill the bacteria at all concentrations. Using a more qualitative broth turbidity method (19), PVP-I showed consistently high activity and complete efficacy in 30 seconds against all the clinical isolates from nosocomial infections among the four antiseptics tested.

The use of in vitro studies to assess the efficacy of antiseptics is sometimes questioned because the laboratory conditions do not accurately represent the clinical setting, although it is argued that trials evaluating antiseptics in vivo can often be subject to extreme variation (13). The in vitro studies reviewed above allow evaluation of the intrinsic antiseptic activity under well-controlled conditions and therefore are equally valuable. In reality, both in vitro and in vivo studies are important in developing an insight into the actual efficacy of these products. The use of povidone–iodine in clinical studies is reviewed in this article with respect to three of its major applications:

(i) Hand-washing and disinfection
(ii) Skin preparation prior to invasive procedures:
  (a) Surgical procedures
  (b) Non surgical procedures: insertion of urinary catheters, intravascular catheters and epidurals and venepuncture
(iii) Antiseptic irrigation

CLINICAL STUDIES ASSESSING THE EFFICACY OF PVP-I

Hand-washing and disinfection

In the 1840s, Ignac Semmelweis recognised that hand-washing, using chloride of lime, between the post-mortem room and the delivery suite could reduce puerperal sepsis almost tenfold, with the British surgeon Joseph Lister ushering in a new era of antiseptic surgical technique in 1860. The skin flora present on the hands can be divided into transient flora ('contaminating flora') or resident flora ('colonising flora'). The former are micro-organisms isolated from the skin and are not shown to be consistently present in the majority of people (10) but are readily transmissible. Resident flora consists of micro-organisms persistently isolated from the skin of most people, for example coagulase-negative staphylococci, diphtheroids, *Propionibacteria* spp.

Three main modes of hand disinfection can be identified (10,20):

(i) Hand-washing is the process for the removal of soiling and dirt from the hands, usually with soap and water. The mechanical action can also remove and reduce the density of transient flora
(ii) Hygienic hand disinfection or hand antisepsis is the process by which transient micro-organisms are removed or destroyed. It kills and eliminates most transient flora and is used for disinfection after contamination of hands
(iii) Surgical hand disinfection or 'surgical scrubbing' is used preoperatively to remove or destroy transient micro-organisms and reduce the resident flora

The use of povidone–iodine will be reviewed in the context of the latter two modes of use.

Hygienic hand disinfection

An effective antiseptic for hand disinfection needs to target a wide range of micro-organisms and be effective within 1 minute – an effect against the resident flora, or a sustained action is not necessary (21). The efficacy of povidone–iodine liquid soap (0·75% PVP-I), 4% CHX and 60% isopropanol and *n*-propanol rub was compared for the disinfection of hands that were artificially contaminated with the test organism *Escherichia coli* (21). The average log reduction factor of microbial colonies before and after test was highest in the alcohol groups, with povidone–iodine found to be slightly more effective than CHX. The advantages of alcohol include the speed of drying and that an application for just 20–30 seconds can be sufficient for routine hygienic hand disinfection (20). The use of a waterless, alcohol-based hand rub was found to increase compliance with hand hygiene at the bedside (22). However, it has been shown that alcohol gels do not meet the efficacy requirements within 30 seconds of application (23), and their widespread use could result in increased risk of transmission because the application time in daily practice averages only 8–15 seconds (22).

Ten per cent PVP-I, 4% CHX detergents, alcohol-based solution and unmedicated soap have been evaluated in clinical practice (24). The health care workers involved used different hand hygiene techniques, using these agents in random order immediately after patient care activity, and the fingertips of the dominant hand were pressed onto agar culture before and after each technique. Bacterial reduction after hand-washing with antiseptic-based solutions or hand-rubbing with alcohol solution was significantly greater than that after using unmedicated soap; but there was no significant difference between the PVP-I, CHX and the alcohol-based disinfectants.

In a study (25) comparing efficacy of 14 hand-washing preparations in laboratory tests, the test organism *E. coli* was applied to fingertips and log reduction factors were measured before and after hand-washing with several agents. This study also showed that alcoholic preparations, particularly *n*-propanol and isopropanol, were the most effective. CHX and PVP-I detergents were significantly more effective than non medicated soap, and the former had the best residual activity over time. However, the above studies only evaluated one test organism, but other micro-organisms, particularly *S. aureus*, which are also important in health-care-associated infections (HAIs), were not tested.

MRSA remains an important cause of HAI, and hand-washing is one of the most important preventative measures in reducing transmission (26). In a study (27) comparing plain liquid soap, ethyl alcohol 70%, 10% PVP-I liquid soap and 4% CHX detergent, the removal rates of a hospital strain of MRSA from artificially contaminated hands were evaluated, and 10% PVP-I was found to be the most effective agent. Of note, CHX was found to be significantly inferior to even plain liquid soap. The alcohol was applied by pouring into cupped hands and rubbing palm to palm for 30 seconds and then allowing the hands to dry for 30 seconds. The other agents were applied in the same way, but hands were pre-moistened with sterile water and rinsed after application for 15 seconds and then dried with sterile towels for 15 seconds. Obviously, these strict hand disinfection protocols may not be practical in the clinical setting, and therefore, results may not reflect the efficacy of agents in 'everyday' clinical scenarios.

However, other studies have shown the efficacy of PVP-I against MRSA in vitro (15,28), and in a similar clinical study, it was found that 7·5% PVP-I reduced the counts of MRSA applied to the fingertips by over 99% (29). In clinical studies (27,29), the alcohol rub was found to be similar in efficacy to PVP-I against MRSA, and the limited efficacy of CHX against MRSA has also been confirmed by other studies (30,31).

Another organism that has become important in high-risk clinical environments, such as the intensive therapy unit (ITU) or high dependency unit, is *Acinetobacter baumannii*, particularly because of its increasing resistance to a wide range of antibiotics and its ability to survive for long periods. It has been shown that ethyl alcohol and 10% PVP-I had significantly higher removal rates of the test organism from artificially contaminated hands than plain soap or 4% CHX (32).

Surgical hand disinfection

Surgical hand scrub is used to remove the transient flora and reduce the resident flora for the duration of operative surgery in case of glove tears. Therefore, the evaluation of efficacy needs to consider disinfection not only immediately after application but also after wearing gloves for a period that should cover the duration of most operations; this continued anti-microbial activity reflects the 'persistent' effect of an antiseptic agent. A 5-minute scrub with 7·5% PVP-I, a 3-minute scrub with 4% CHX detergent and 5-minute rubbing of 60% *n*-propanol or isopropanol were evaluated and showed that immediately after disinfection, *n*-propanol was the most effective (LRF 3·43) in reducing resident flora, with PVP-I (LRF 0·92) slightly more effective than CHX (LRF 0·78) (21). After wearing a surgical glove for 3 hours, a mean reduction factor of only 0·24 was attributed to PVP-I, suggesting virtually no sustained effect. In contrast, CHX exerted a marked sustained effect, which was significantly better than PVP-I but significantly inferior to that of isopropanol. The persistent effect of CHX has been shown in other studies (33,34), and the use of CHX has been suggested as a means of reducing the scrub time for subsequent cases because of this persistent effect (35).

However, povidone–iodine is still one of the most commonly used surgical scrub preparations, and a study (36) investigating the factors affecting surgical disinfection with this product found that a scrub of at least 3 minutes should be performed to attain effective disinfection. Others have observed no significant difference in bacterial colony counts between long (5-minute initial scrub and 3-minute consecutive

Key Points

- it has been shown that hand washing with ethyl alcohol and 10% PVP-I had significantly higher removal rates of the test organism from artificially contaminated hands than plain soap or 4% CHX

Key Points

- all of the surgical hand disinfection agents are effective; the preference for one over the other is usually based on individual preference, particularly based on tolerance towards the agent
- it should be emphasized that whatever agent is selected, the agent should be applied strictly according to the manufacturer's guidelines to ensure maximum efficacy
- the reduction of the level of resident flora from the patient's skin using antiseptics is also an important step prior to surgery because these commensals can lead to wound infection if allowed to multiply to a level that overcomes the host defences at the incision site

scrub) and short (3-minute initial scrub and 30-second consecutive scrub) scrubs when PVP-I was used (37). In contrast, the longer duration scrub was more effective with CHX, and although there was no difference in bacterial counts between 4% CHX and 7·5% PVP-I initially, overall, both long- and short-duration scrubs, with CHX, maintained significantly lower microbial numbers than PVP-I over time. The action of the long-duration CHX scrub (5-minute initial scrub and 3-minute consecutive scrub) was found to be the most effective regimen.

In a clinical trial (38), using 30-day surgical site infection (SSI) rates as the primary endpoint, it was found that a protocol of hand-rubbing with 75% aqueous alcoholic solution, preceded by a non antiseptic soap wash, was as effective as that using 4% PVP-I or 4% CHX 'traditional' scrubs, with better compliance and tolerance for the alcoholic hand-rubbing protocol.

Although the majority of the studies seem to support the use of alcohol rubs over CHX or povidone–iodine, it is very difficult to firmly conclude in favour of one agent over another. There is no general agreement on testing techniques to be followed, and results are often expressed in different ways, making it difficult, if not impossible, to make valid comparisons between studies or combine the results of studies. Clearly, all these agents are effective surgical hand disinfection agents; the preference for one over the other is usually based on individual preference, particularly based on tolerance towards the agent. It should be emphasised that whatever agent is selected, the agent should be applied strictly according to the manufacturer's guidelines to ensure maximum efficacy.

Skin preparation prior to invasive procedures

Surgical procedures

SSIs remain an important complication of surgical practice; they can prolong hospital stays with significant associated morbidity and mortality (39). One of the many methods of preventing SSI includes preparation of the patient's skin prior to surgery because the majority of infections are acquired intra-operatively from the patient's endogenous flora that colonise the patient's own skin, gastrointestinal tract or mucous membranes. Preoperative skin preparation aims to rapidly reduce the soil and transient flora from the skin (40). The reduction of the level of resident flora from the patient's skin using antiseptics is also an important step prior to surgery (39–41) because these commensals can lead to wound infection if allowed to multiply to a level that overcomes the host defences at the incision site (42).

The antiseptic of choice therefore needs to be rapidly acting, broad spectrum and also persistent to suppress regrowth of remaining organisms during the course of the operation. Although aqueous PVP-I solution is broad spectrum and shows some level of persistence (43), it may require several minutes to reach a maximal effect as suggested by the manufacturer's recommended application time of 3–5 minutes. Furthermore, because of their aqueous nature, such antiseptics can take longer to dry after application (43).

In an early study, cultures of microbial flora were obtained from the skin at the operation site preoperatively and following preparation with PVP-I (44). In this study of 150 patients, the absence of postoperative infections and the decrease in microbial populations after application of PVP-I indicated that it was a reasonable preoperative antiseptic agent.

The traditional skin preparation method involved a 5- to 7-minute povidone–iodine scrub, followed by painting with povidone–iodine solution. However, this technique was found to be time consuming and expensive (45). Several studies have shown that the scrubbing phase can be eliminated altogether, in favour of paint with aqueous povidone–iodine alone, without changing the efficacy (45–50). In UK, skin preparation is usually undertaken by applying antiseptic solution with friction over the operation site and over surrounding areas for 3–4 minutes using a sterile gauze swab. The antiseptic solution must be allowed to dry, particularly with alcoholic solutions, to prevent the risk of burns associated with pooling of antiseptic and the use of electrosurgical equipment.

An alternative skin preparation method has been evaluated (51); 64 patients undergoing elective vascular surgery involving groin exposure were randomised to twice-daily skin preparation with 10% aqueous PVP-I for 48 hours preoperatively, followed by 10% PVP-I paint prior to surgery in theatre or 10% PVP-I prior to surgery in theatre alone. There was no significant difference in the incidence of postoperative groin wound infection between the two groups, suggesting no additional benefit of regular application of PVP-I solution for 48 hours prior to surgery.

Prior to cardiothoracic surgery, various preoperative skin preparation regimens were evaluated for the prevention of sternal SSIs in patients at high risk of developing infection (52). A total of 209 patients were randomised into four groups: PVP-I paint only, a 5-minute PVP-I scrub and then paint, one-step iodophor/alcohol water-insoluble film and one-step iodophor/alcohol water-insoluble film with iodine-impregnated incise drapes. There was no statistically significant difference in the rate of sternal SSIs between these four groups. However, when the two aqueous iodine groups were combined and the two alcoholic insoluble iodine groups combined retrospectively, fewer patients in the latter group developed sternal SSIs, and this was statistically significant.

Alcohol is an excellent disinfectant, with a rapid action against a broad spectrum of micro-organisms, and dries quickly. However, once evaporated, it has no persistent effect, whereas PVP-I provides more persistent activity over time. A new formulation of PVP-I in a gel form containing 5% PVP-I and 62% ethanol [PVP-I gel alcohol (PGA)] has been designed to combine the attributes of both antiseptics to increase efficacy and has been evaluated as a 30-second, one-time application preoperative skin preparation by both in vitro and in vivo methods. It was found that the formulation delivered a rapid antimicrobial activity in vitro, reducing challenge organisms of all 33 species to below detection level within 30 seconds (53). Clinically, a 30-second application was as effective as a 5-minute PVP-I preoperative scrub in reducing normal skin flora at inguinal and abdominal sites. Furthermore, PGA was effective in controlling bacterial growth for at least 24 hours at both sites, in contrast to alcohol gel without PVP-I or PVP-I gel without alcohol.

Another study (54) compared the efficacy of povidone–iodine alcoholic solution with povidone–iodine aqueous solution by assessing LRF in resident bacterial counts before and after preparation and found that significantly greater reduction factors were obtained with the use of povidone–iodine alcoholic solution.

The advantages of combination alcohol and PVP-I formulations include shorter application and drying times as a result of the contained alcohol and easier recognition of areas that have been prepped as a result of the staining characteristics of iodine, in contrast to clear formulations such as CHX. However, disadvantages include the flammable nature of the alcohol and in some cases, such as cosmetic surgery, the staining of skin may be a problem (43).

Few studies have directly compared the efficacy of different antiseptics as preoperative skin preparation. A randomised controlled trial comparing 10% PVP-I and 4% CHX in skin preparation was conducted prior to vaginal surgery (55), and cultures of the vaginal field were obtained prior to preparation, 30 minutes after skin preparation and hourly thereafter throughout surgery. Based on cultures obtained at 30 minutes, CHX was found to be significantly superior, with cultures from the PVP-I group more than six times as likely to be contaminated. However, no significant differences were found at later time-points. Other studies also suggest that CHX may be a more effective skin disinfectant than PVP, and its use results in lower mean colony counts of skin bacteria at the surgical incision site (56–58). However, these studies evaluated regimens using preoperative showers rather than using preoperative skin painting.

In an early study, the efficacy of 10% PVP-I in alcoholic solution and 0·5% CHX in spirit was assessed as preoperative skin preparations by comparing postoperative wound infection rates in a prospective, randomised study of 866 patients (59). There was no significant difference in SSI rates at a standard observation of 3–4 days postoperatively.

An interesting study evaluated the use of povidone–iodine in a developing country (60) to determine whether the added expense of importing PVP-I for operative skin preparation would result in lower wound infection rates in clean hernia operations. The study involved 200 patients randomised to preparation with inexpensive market soap and methylated spirit or imported PVP-I solution. There was no statistically significant difference in the rate of infection between the two groups, and this highlights that choice of antiseptic is only one factor among many that affect wound outcome and the development of an SSI.

A Cochrane review has been undertaken, which evaluated all randomised controlled trials comparing the use of different skin

Key Points

- a new formulation of PVP-I in a gel form containing 5%PVP-I and 62% ethanol [PVP-I gel alcohol (PGA)] has been designed to combine the attributes of both antiseptics to increase efficacy and has been evaluated as a 30-second, one-time application preoperative skin preparation by both *in vitro* and *in vivo* methods

Key Points

- septicaemia is an important life-threatening complication in patients who have vascular catheters (61), and heavy colonisation of the insertion site is highly predictive of catheter-associated sepsis; antiseptic preparation of the skin before insertion of central venous and arterial catheters is considered an important preventative measure

antiseptics for preoperative preparation in 'clean surgery' (42). Out of the six trials identified, only one study (59) showed a significant difference in infection rates between two different antiseptics (in favour of CHX over PVP-I), but the Cochrane review extracted the 'clean' surgery data alone from this study. Overall, there was no statistical difference between PVP-I and CHX groups when all types of surgery were included in the analysis (59). The Cochrane review (42) also noted that the study was limited because of lack of extensive follow-up and therefore could have underestimated the actual rate of infection in the two groups.

Research into the efficacy of antiseptics is often hampered by small sample sizes, producing weak evidence. Furthermore, it is difficult to combine the results of trials because of varying techniques of skin prepping used and varying concentrations and formulations of the same antiseptic evaluated.

Invasive non surgical procedures

Antiseptic solutions are commonly used for skin preparation prior to the insertion of intravascular and epidural catheters and percutaneous withdrawal for blood cultures. Septicaemia is an important life-threatening complication in patients who have vascular catheters (61), and heavy colonisation of the insertion site is highly predictive of catheter-associated sepsis (62). For this reason, antiseptic preparation of the skin before insertion of central venous and arterial catheters is considered an important preventative measure.

A prospective randomised controlled trial comparing three antiseptics (10% povidone–iodine, 70% alcohol and 2% aqueous CHX) was conducted to evaluate the prevention of infection associated with intravascular catheters in an ITU environment (61). CHX was associated with the lowest incidence of catheter-related infection and this was statistically significant. However, the interpretation of the study has been questioned, and it was argued that a substantial proportion of the catheters was placed at existing catheter insertion sites over a guide wire that could increase the risk of infection, particularly if previous catheters were colonised with bacteria (63). In this second prospective randomised trial (63), the superiority of CHX over povidone–iodine as a pre-insertion skin preparation, in this same clinical environment, was also confirmed with significantly lower catheter colonisation and catheter-related sepsis in the CHX group. The difference was attributed to the larger effect of CHX on prevention of catheter colonisation by Gram-positive bacteria, particularly coagulase-negative staphylococci.

Despite the superiority of CHX over 10% aqueous PVP-I, the latter still remains the most widely used agent for cleansing catheter sites prior to insertion (64). Alcoholic povidone–iodine solution was found to be more effective than the aqueous form in reducing catheter colonisation and resulted in a significantly lower incidence of catheter-related infection (64). A meta-analysis of eight randomised clinical trials comparing CHX with PVP-I for catheter site care was conducted and found that among patients with a central vascular catheter, CHX used for skin disinfection at insertion site reduced the risk for catheter-related bloodstream infection by 49% (65).

An epidural abscess is a serious complication following an epidural block, and a potential source is invasion of skin bacteria through the needle track (66). It has been shown that viable organisms could be isolated from skin specimens after disinfection with 10% PVP-I, and these isolates were found in significantly greater proportion of the skin specimens disinfected with 10% PVP-I than in those disinfected with 0·5% CHX in ethanol (66). The superiority of CHX over PVP-I in disinfection prior to epidural insertion was supported in another study (67), which showed that, in children, continuous epidural catheters inserted after skin preparation with CHX were one sixth as likely and less quickly to be colonised as catheters inserted after skin preparation with 10% PVP-I. Whether this translates to a significantly reduced incidence of catheter-related sepsis is unclear.

An iodophor combined with isopropyl alcohol was found to provide a greater decrease in the number of positive skin cultures, immediately after disinfection, than 10% aqueous iodine alone in a study evaluating bacterial regrowth and colonisation of epidural catheters (68).

The problem of blood culture contamination is widespread. Blood cultures are important for the diagnosis and treatment of bloodstream infections. However, up to 50% of all positive cultures may be positive simply because of the presence of contaminants (69,70) and coagulase-negative staphylococci and other skin flora are the most common contaminants (71). Use of antiseptics prior to venepuncture aims to prevent this contamination. A randomised trial was conducted to compare four antiseptics (10% PVP-I, 70% isopropyl alcohol, tincture of iodine and 10% PVP-I with 70% ethyl alcohol) but found no significant differences in the blood culture contamination rates among these antiseptics (71). In contrast, skin disinfection with an alcoholic solution of 0·5% CHX was found to reduce the incidence of blood culture contamination significantly more than 10% PVP-I (72).

The increased efficacy of CHX in these clinical scenarios could be explained by the fact that it takes several minutes for aqueous PVP-I to provide its maximum antiseptic effect (72), and the interval between skin disinfection and insertion of catheters or venepuncture is relatively short. This may also explain the increased efficacy of PVP-I when combined with an alcohol (64,68).

Antiseptic irrigation

Acute wound irrigation

There have been several studies that have shown the benefit of preventing wound infection by high-pressure irrigation of traumatic wounds (73,74), but one of them found that there was no significant difference in infection rates among sutured wounds irrigated with normal saline, 1% povidone–iodine or Pluronic F-68 solution in the emergency department (75). Another group (76) conducted a prospective randomised trial of patients undergoing a range of general surgical procedures, in which wounds were irrigated with either 10% PVP-I or normal saline prior to closure; for all types of wounds, there was a significantly lower incidence of wound infections in the PVP-I irrigated group. In a series of paediatric surgical patients (77), 1% PVP-I irrigation of appendectomy wounds, prior to closure, resulted in significantly fewer wound infections compared with that in the normal saline group, unless peritonitis or a periappendicular abscess was already established. However, in patients undergoing vaginal hysterectomy (78) PVP-I, used as a vaginal irrigant, was no more effective than normal saline in preventing wound infection.

There appears to have been little work on the value of iodine products in open, acute wounds, being managed by allowing healing through secondary intention. The further development of slow, sustained release of iodine, using different delivery systems such as cadexomer iodine (Iodosorb), hydrosomes or other composite dressings could have value in this area, particularly as they may offer less toxicity to the wound. As an example, deep wound infection can be a devastating complication following spinal surgery. In a prospective randomised trial of 414 patients undergoing spinal surgery, surgical wounds were irrigated with 3·5% povidone–iodine, followed by normal saline in a treatment group or normal saline alone in a control group (79). The incidence of deep infection and total infection rate was significantly lower in the PVP-I irrigation group. The use of a slow-release iodine preparation could have facilitated this care.

Key Points

- the incidence of deep infection and total infection rate was significantly lower in the PVP-I irrigation group. The use of a slow-release iodine preparation could have facilitated this care

Bladder irrigation

Povidone–iodine has also been used as continuous bladder irrigation during catheterisation in patients having urological procedures and was shown to reduce catheter-associated urinary tract infections (80). A randomised controlled trial (81) showed that bladder irrigation with PVP-I after single or intermittent urethral catheterisation in orthopaedic patients resulted in a significantly lower incidence of hospital-acquired bacteriuria. In another randomised study, it was found that bladder irrigation with PVP-I prior to removal of an indwelling catheter did not significantly reduce the incidence of subsequent bacteriuria in comparison with controls (82).

Intra-peritoneal irrigation

Surgical procedures involving heavy bacterial contamination of the peritoneal cavity can lead to peritonitis, intra-abdominal abscess or sepsis with multiple organ failure and a high mortality. In a prospective randomised study (83), the use of dilute PVP-I solution as an intra-peritoneal irrigant in patients undergoing laparotomy was found to be significantly superior to saline irrigation in preventing the development of intra-abdominal abscesses. It was noted that serum iodine levels were elevated for 24 hour post-irrigation with PVP-I, although they returned to near normal by 72 hours. There has been caution in the use of PVP-I as an intra-peritoneal irrigant because of the concerns of this toxicity and excessive absorption of iodine from the peritoneal surface in clinical and animal studies (84–87). The heavy molecular weights of the PVP polymers could impair renal clearance, and so the use of low-molecular-

Key Points

- in clinical environments, there is no general agreement regarding the 'best' antiseptic and practice varies widely
- it is difficult to conduct large randomised controlled trials evaluating antiseptics, not only in the wide range of clinical environments but also because of the need to incorporate adequate follow-up and clinically meaningful outcome measures
- this review shows that this available evidence varies in its support of povidone–iodine as the antiseptic of choice and, despite the antimicrobial efficacy of povidone–iodine, may be dependent on the clinical indication for its use
- further research using iodine preparations in open acute wounds could concentrate on the value and development of slow-release delivery systems

weight (LMW) Betadine solution (10% PVP-I) was evaluated as an intra-peritoneal irrigant in surgical procedures, which were considered likely to encounter bacterial contamination of the peritoneal cavity (88). The study concluded that LMW PVP-I could reduce the incidence of intra-abdominal infectious complications when used as an intra-peritoneal irrigant. Although serum iodine levels rose by about nine times the levels in the saline group at 24 hours, they normalised 1 week postoperatively and no signs of iodine toxicity were found.

Bowel irrigation

In a randomised trial (89), preoperative bowel irrigation with 10% PVP-I in patients undergoing major resection for large bowel carcinoma was found to be more effective than bowel irrigation with water in reducing abdominal wound infection. The efficacy of colonic irrigation with PVP-I is further supported by a 10-year retrospective review of 367 patients undergoing colonic resection and anastomosis (90). Patients with colorectal cancer can have a large number of viable cells in the lumen of their colon (91), and surgical implantation of these may be a possible cause of local recurrence (92). Povidone–iodine is commonly used as an intra-luminal agent in patients undergoing resection for large bowel cancer to prevent anastomotic recurrence (93), and studies have found that PVP-I is an effective cytotoxic agent against tumour cells in vitro and in vivo (92). Furthermore, a study (94) evaluating thyroid function and systemic absorption of iodine after intra-rectal irrigation of PVP-I, in patients undergoing colorectal surgery, found that the high serum levels of iodine did not cause organ toxicity and concluded that a single use of intra-operative bowel irrigation with PVP-I could be performed with negligible risk.

SUMMARY

The review has highlighted the background properties of povidone–iodine in relation to its principal use as a topical antiseptic agent and complements a separate review of the use of iodine-containing products in chronic wound care (95). Povidone–iodine has been evaluated over several decades using a range of formulations in a wide range of settings, both in vitro and in vivo. The broad antimicrobial spectrum of povidone–iodine is well documented and its efficacy, particularly in relation to resistant micro-organisms such as MRSA, has been shown. However, in clinical environments, there is no general agreement regarding the 'best' antiseptic and practice varies widely; indeed, most guidelines in relation to hand-washing and preoperative preparation avoid definitive recommendations with regard to the choice of agent. Depending on the environment involved, povidone–iodine has advantages and disadvantages as highlighted by the above studies. Significant influences on the choice of agent also arise from many other factors, including personal tolerance to the agent (e.g. skin irritation).

Unfortunately, it is difficult to conduct large randomised controlled trials evaluating antiseptics, not only in the wide range of clinical environments but also because of the need to incorporate adequate follow-up and clinically meaningful outcome measures. This is reflected in the relative paucity of acceptable reported studies, which also present variable findings, but without such 'gold-standard' evidence, health care workers should assess the 'next best available' evidence. This review shows that this available evidence varies in its support of povidone–iodine as the antiseptic of choice and, despite the antimicrobial efficacy of povidone–iodine, may be dependent on the clinical indication for its use. Further research using iodine preparations in open acute wounds could concentrate on the value and development of slow-release delivery systems.

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